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Friedman Recognized for Pioneering Gene Therapy Research

School of Medicine professor receives prestigious Japan Prize

Theodore Friedmann, MD, professor in the Department of Pediatrics at University of California, San Diego School of Medicine was named today one of three recipients of the 2015 Japan Prize, a prestigious international award honoring laureates whose “original and outstanding achievements in science and technology have advanced the frontiers of knowledge and served the cause of peace and prosperity for mankind.”

Theodore Friedmann

Friedmann is being recognized for his pioneering research and contributions to the development of gene therapy, a new field of medicine which in significant ways originated at UC San Diego. The sponsoring Japan Prize Foundation describes Friedmann as “the father of gene therapy.”

Sharing the 2015 Japan Prize “in the field of medical science and medicinal science” with Friedman is Alain Fischer, MD, PhD, director of immunology at the Necker Hospital in Paris, France. Fischer is credited with demonstrating the clinical efficacy of gene therapy by successfully treating children suffering from a severe genetic disorder that renders them extremely vulnerable to infections.

The third 2015 Japan Prize laureate is Yutaka Takahasi, PhD, professor emeritus at the University of Tokyo, who is being honored in the “field of resources, energy and social infrastructure” for his contributions to river basin management and reducing water-related disasters.

Each laureate will receive a certificate of recognition and commemorative gold medal. A cash award of approximately $416,600 will also be given to each prize field. Since its inception in 1985, 83 laureates from 13 countries have received the Japan Prize in a variety of fields and disciplines. Several have subsequently become Nobel Prize laureates as well.

In 1972, Friedmann, then a visiting scientist at the Salk Institute for Biological Sciences in La Jolla, and Richard Roblin, also at the Salk Institute and a post-doctoral fellow out of James Watson's lab at Harvard University, published a foundational article in the field, a paper in the journal *Science* under the heading "Gene therapy for human genetic disease?"

Though posed as a question, Friedmann and Roblin firmly believed the answer was yes, citing emergent thinking, new studies and growing data that suggested "good DNA" could be used to replace defective DNA in people with inherited conditions.

"In our view," they wrote, "gene therapy may ameliorate some human genetic diseases in the future. For this reason, we believe that research directed at the development of techniques for gene therapy should continue."

Though Friedmann said initial response to the paper was "not overwhelming," it's now commonly cited as a major milestone in the scientific beginnings of gene therapy research, though Friedmann said it was the Asilomar conference three years later (scientists set safety standards for recombinant DNA technology) where interest really "exploded."

The idea of gene therapy, which quickly captured the public imagination, was fueled by its appealingly straightforward approach and what Friedmann has described as "obvious correctness": Disarm a potentially pathogenic virus to make it benign. Stuff these viral particles with normal DNA. Then inject them into patients carrying abnormal genes, where they will deliver their therapeutic cargoes inside the defective target cells. In theory, the good DNA replaces or corrects the abnormal function of the defective genes, rendering previously impaired cells whole, normal and healthy. End of disease.

It's not quite that simple, of course, something Friedmann and Roblin had cautioned in their 1972 paper. Despite progress in the understanding of cellular functions, the roles of DNA and a series of experimental and clinical advances, the history of gene therapy has been marked by distinct highs and lows.

In 1968, Friedmann, working at the National Institutes of Health in Bethesda, Maryland with the late Jay Seegmiller (a founding faculty member of the School of Medicine) and others, showed that by adding foreign DNA to cultured cells from patients with Lesch-Nyhan syndrome, they could correct genetic defects that caused the rare but devastating neurological disorder. The condition was first described by William Nyhan, MD, a UC San Diego professor of pediatrics, and medical student Michael Lesch in 1964.

The feat was a powerful proof-of-concept, but subsequent efforts to advance the work to human clinical trials stalled. "We began to realize that it would be very complicated to take this idea and make it work in people," Friedmann said, who joined the School of Medicine faculty in 1969.

In 1990, a 4-year-old girl with a congenital disease called adenoside deaminase (ADA) deficiency, which severely affects immunity and the ability to fight infections, became the first patient treated by gene therapy. White blood cells were taken from her, the normal ADA gene was inserted into them using an engineered and disabled virus and the cells re-injected. Despite initial claims of success, Friedmann said the experiment was eventually deemed a failure. The girl's condition was not cured, and the research was found wanting.

A report commissioned by National Institutes of Health director Harold Varmus, MD, was highly critical of the entire gene therapy field and the ADA effort in particular, chiding investigators for creating a "mistaken and widespread perception of success." Friedmann says he took the Varmus report "personally. I felt awful. It almost made me feel like I had been deceiving myself and my colleagues for more than two decades about the promise of gene therapy." But he also knew there were "many more good people doing gene therapy research than rogues" and continued diligently and conscientiously to pursue his own research.

Nonetheless, media attention and hype about gene therapy continued to be rampant, fueled in part by over-enthusiastic opinions by some scientists. Things crashed in 1999 when an 18-year-old patient named Jesse Gelsinger, who suffered from a genetic disease of the liver, died during a clinical trial at the University of Pennsylvania. Gelsinger's death was the first directly attributed to gene therapy. Subsequent investigations revealed numerous problems in the experimental design.

Friedmann said he has long realized that eventual success of gene therapy could not stop with a good idea and with good laboratory results but would require truly careful, rigorous and imaginative clinical studies. "That's happened – and the field has moved greatly in the past decade." Friedmann's efforts have focused on development of improved virus gene transfer tools. He is pursuing studies on the application of current genetic knowledge and stem cells models to try to understand the basis for Lesch-Nyhan and identify more accessible treatment targets for gene-based and other forms of therapy. He continues to be a staunch advocate for rigorous gene therapy science elsewhere.

"Technology has gotten better. New kinds of viruses, such as the lentiviruses (a more efficient and safer gene delivery vector) were created. Disease models expanded. The science got more rigorous. I think the Japan Prize Foundation's decision to honor Dr. Fischer and myself is even greater recognition of the field itself, how far it has come and how much promise it holds."

In recent years, researchers in Europe and elsewhere have reported successfully treating children with SCID, a dramatic genetic disorder characterized by the lack of an immune response. These patients are extremely vulnerable to infectious diseases; previously, children with the condition had to live in highly sterile environments to avoid exposure to life-threatening infections or to undergo bone marrow transplantation. Friedmann noted that clinical trials for other conditions, such as forms of blindness, degenerative brain diseases, hemophilia and some metabolic diseases, are also proving effective and evolving rapidly into important treatments.

He added that the basic concept gene therapy – genetic correction – is now being expanded to include even more definitive methods to correct the abnormal spelling of mutated, disease-causing genes – an approach called “genome editing.”

“We’re well past the stage of having to prove the concept of gene therapy and have finally overcome our history of perhaps promising too much too soon. We’re at the point where we can truly begin to deliver real treatments to real people.”